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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,055	BELMANT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-93 and 95-118* is/are rejected.

7)☒ Claim(s) *94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 2/27/04.

Claims 29-84 were canceled and new claims 85-118 were added as requested.

Claims 85-118 are pending and under consideration in this Office Action.

Note that this Action includes a new ground of rejection, and is therefore NON-FINAL.

Specification

The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c). See page 24, line14, and page 34, line 23. A properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required.

Response to Arguments

Applicant's arguments filed 2/27/04 have been considered but are unpersuasive.

Applicant states that "the alterations specification were a result of a printer error. As a result, applicants do not believe that the alterations need initialed and/or dated as required by 37 CFR l.52(c)". This is unpersuasive because 37 CFR 1.52© makes no allowance for printer errors, instead it states that "[a]ny interlineation, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying oath or declaration pursuant to § 1.63 referring to those

application papers and should be dated and initialed or signed by the applicant on the same sheet of paper." For this reason the objection is maintained.

Claim Objections

Claim 85 and dependents are objected to. In claim 85, "Tγ9δ2 lymphocytes" should be made singular, or "a Tγ9δ2 lymphocyte" should be made plural so that the method steps agree with the purpose set forth in the preamble. If Applicant chooses to make "Tγ9δ2 lymphocytes" singular, then the same change should also be made to claims 86 and 89.

The word "and" should be inserted after "cation" in claims 85 and 96.

It is suggested that the word "into" should be substituted for the word "in" in claims 88 and 89. Alternatively, for claim 89, the word "contacted" could be substituted for the word "introduced" to make the language more consistent with claim 85.

Claim 93 is objected to because "corporal" is misspelled.

Claim 97 is objected to because 'Ts' is not defined.

Claims 97 and 115 are objected to because formula (14) is missing an oxygen atom between the terminal phosphorous and R2. Compare to e.g. the specification at page 12, line 34.

In claim 98, "said compound" should be substituted for "said composition".

Claim 117 is objected to because it is ungrammatical. Deletion of "in" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 97-115 are indefinite because they fail to adequately define 'R2'. More particularly the metes and bounds of "a compound allowing the formation of a compound of the formula [structure comprising R2] (14)" are unclear. For example, it is unclear what are the starting materials from which one is to form structure 14. As such, it is unclear what compounds can allow the formation of the structure. It is suggested that the claims should be amended to include the starting material, i.e. structure (11) found at page 12 of the specification. These claims are also indefinite because it is unclear to what "the latter" refers, immediately after structure (15). The antecedent for "the latter" appears to be structure (15), yet the claim then requires that "the latter" must be chosen from a Markush group that does not comprise structure (15). Also the two members of this Markush group are not separated by a conjunction. Similarly, Markush group species a), b), and c) are not separated by a conjunction.

Claims 98, 100-102, and 104 are indefinite because although they are drawn to compositions, they recite only a single component. A composition is considered to be an article of matter that comprises at least two components, as such these claims must recite at least one other component.

Claim 101 is indefinite because it is unclear what are the metes and bounds of "a general route". The specification does not give this term a limiting definition, and a search of the prior art did not reveal it as a term of art, thus one of skill in the art could not know the metes and bounds of the claim.

Claims 107-114 are indefinite because it is unclear what are the intended members of the Markush group. If Applicant intends structure '(5)' to be an alternative in the Markush group, then it is suggested that it should be labeled as 'c)', because the first two members of the Markush group are labeled 'a)' and 'b)'.

Claim 115 is indefinite because it is a process claim that recites no steps. Also the claim requires formula '(5)' to be both the starting material and the finished product. It is suggested that the phrase "it is used as a compound," should be deleted and the word "starting should be inserted between the word "a" and "compound" so that the two lines of the claim immediately after structure (15) would read:

"according to claim 97, wherein a starting compound is selected from the group consisting of".

However, it would be better to delete the claim entirely and rewrite it to incorporate reaction schemes 1, 2, and 3 from pages 12-14 of the specification. This would solve the problem of the claim lacking method steps, and would clarify the starting materials and products.

Claims 116 and 117 are indefinite because nucleosides and phosphoepoxides are not inorganic compounds.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 97-115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to the genus of compounds R2 that allow formation of a compound of structure (14). As such, the claimed genus of compounds is described by functional limitations, not by structural limitations, and the breadth of the genus is unknown.

When examining genus claims for adequate written description, one must determine whether or not a representative number of species of the claimed genus has been described. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and

> knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The instant specification sets forth several classes of compounds within the claimed genus, e.g. nucleoside derivatives, oligonucleotides, nucleic acids, amino acids, peptides, proteins, mono-, oligo-, and polysaccharides, fatty acids, folic acid, tetrahydrofolate, phosphoric acids, inositol, vitamins, co-enzymes, flavonoids, aldehydes, halohydrins, phosphoepoxides, and epoxides. Of these, a nucleoside, and a phosphoepoxide are reduced to practice. See e.g. Examples 3 and 4 at pages 30-32. Although several classes other than phosphoepoxides and nucleosides are listed in the specification, there is no disclosure of correlation between the structure and function of the claimed genuses, i.e. the specification fails to describe what structural characteristics are required to meet the claimed functional requirements. As a result, the breadth of the claimed genus is unclear, and it cannot be said that a representative number of species has been described. However, because the specification discloses a wide variety of biomolecules, i.e. nucleic acids, lipids, proteins, and carbohydrates, it is suggested that the term “biomolecules” has support in the specification as filed. It is further suggested that claim 97 should be amended to define ‘R2’ as a biomolecule. For example, “biomolecule” could be substituted in claim 97 for “substituent”, and for the first instance of “compound” in item “a)”.

Scope of Enablement

Claims 85-93, 95, 107-114, and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of activating Tγ9δ2 lymphocytes in vitro, does not reasonably provide enablement for activating Tγ9δ2 lymphocytes in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors.

Nature of the invention and Breadth of the claims

Claims 85-93, 95, 107-114, and 118 are broadly drawn to methods of activating Tγ9δ2 lymphocytes, in vitro or in vivo. The specification teaches that Tγ9δ2 lymphocytes may be activated in vitro for the purpose of studying the activated cells. See page 20, lines 1-6. When used in vivo, the method may be for therapeutic use (page 20, lines 6 and 7) or for diagnostic use (page 20, lines 29-32). The scope of therapeutic uses is broad and embraces both preventative and curative embodiments (page 20, lines 29-32). The scope of treatable diseases includes conditions belonging to the group comprising cancers, infectious diseases, in particular mycobacterial infections (leprosy, tuberculosis etc.), parasitic conditions (malaria etc.), and pathological immunodeficiency syndromes (MDS etc.) The specification also teaches that Tγ9δ2 cells can be activated ex vivo and then used for therapy. Use activated T-cells for therapy is known in the art as adoptive immunotherapy.

State of the prior art

Yamaguchi et al (J. Immunol. Met. 205(1): 19-28, 6/23/97) taught that gamma delta T cells make up no more than 10% of peripheral blood mononuclear cells, but appear to play an important role in host defense against tumor growth. In order to evaluate their functional activity against tumors, large quantities of cells are required. Yamaguchi taught a method of producing large quantities of gamma delta T cells by isolating them inducing TCR/CD3-mediated signal transduction by contacting the cells with an anti-CD3 antibody and IL-2. Yamaguchi noted that this method may make it possible to produce sufficient numbers of gamma delta T cells for clinical trials of anti-tumor adoptive immunotherapy. See abstract. Thus it was recognized in the art at the time of the invention that obtaining a sufficient number of gamma delta T cells was an obstacle to adoptive immunotherapeutic methods relying on these cells. Although Yamaguchi taught a potential solution to this problem, it was clear that those of skill in the art would not be convinced that the teachings of Yamaguchi were sufficient to solve the problem. For example, Janssen et al (J. Immunol. 146(1): 35-39, 1/1/91) taught that stimulation of gamma delta cells with anti-CD3 antibody and IL-2 led ultimately to cell death through apoptosis, thus calling into question the usefulness of this method for expanding gamma delta cells to the numbers needed for therapeutic purposes. Indeed Lopez et al (Blood 96(12): 3827-3837, 12/1/2000) taught that the exploitation of gamma delta T cells for therapeutic ends remained largely unrealized because of the extreme difficulty in obtaining sufficient quantities of these cells. Lopez noted that while treatment of gamma delta T cells with anti-CD3 or anti-TCR antibodies is an attractive

means of expanding these cells, this method results in apoptosis, thereby presenting a serious obstacle to developing approaches to incorporate gamma delta T cells into any form of adoptive immunotherapy. See page 3827, column 2, lines 2-18. Lopez concluded, "[w]hether γδ-T cells have therapeutically exploitable biologic properties such as antiviral, antitumor, or hematopoietic stem cell graft-facilitating effects, remains to be determined." See page 3836, column 2, lines 5-8. Lopez indicates that amounts of cells far in excess of 10^9 would be needed for therapeutic purposes. See page 3836, lines 7-17.

A search of the prior art revealed no instances of complete disease prevention or cure through the use of Tγ9δ2 cell adoptive immunotherapy.

Unpredictability in the art

The teachings of Janssen (1991) and Lopez (2000) above show that at the time of the invention, the art of adoptive immunotherapy using Tγ9δ2 cells was highly unpredictable, essentially because of the technical difficulty in obtaining sufficient numbers of apoptosis-resistant cells. Furthermore, even if a sufficient number of cells could be obtained, it was not predictable that these cells would be useful for any therapeutic method. See page 3836, column 2, lines 5-8.

Guidance and exemplification in the specification

The specification teaches how to make phosphoepoxide compounds and demonstrates that they can be used to stimulate proliferation of Tγ9δ2 cells in the presence of IL2. See e.g. pages 25-33 of the specification. The specification fails to teach the production of quantities of Tγ9δ2 cells approaching 10^9, and fails to provide

any information as to the mechanism of Tγ9δ2 cell proliferation, or any apoptotic effects of phosphoepoxide-mediated mitogenesis. The specification provides no working example of any therapeutic use of the clamed methods. The specification also provides no guidance as to how to use the claimed methods for any in vivo diagnostic purpose.

Amount of experimentation required

Due to the unpredictable nature of the art of Tγ9δ2 cell adoptive immunotherapy, the recognition in the art that larger numbers of Tγ9δ2 cells were required for therapy than could be produced by existing methods, the failure of the specification to teach how to produce sufficient numbers of cells for therapeutic purposes, and whether or not these cells are subject to apoptosis, particularly in view of their treatment with IL2, one of skill in the art would have to perform undue experimentation to use the claimed compositions for therapeutic purposes as required by the claims. In addition, although the specification teaches that the claimed methods may be used in vivo for diagnostic purposes, the specification gives no guidance or examples in this regard, and it is not immediately apparent how one could use the claimed methods for diagnostic purposes in vivo. This rejection can be overcome by limiting the claimed methods to the scope of in vitro.

Conclusion

No claim is allowed. Claim 94 is objected to for minor informalities. All claims are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.